Sex-Related Differences in Hypertension

Seek and Ye Shall Find

Kate M. Denton, Lucinda M. Hilliard, Marianne Tare

Much of what we understand about the regulation of arterial pressure and extracellular fluid volume has been derived from studies in men. Although the responses that can be mounted against major physiological challenges to extracellular fluid volume (hemorrhage/dehydration) are essentially similar in men and women, there are marked sex-related differences in the regulation of renal and cardiovascular physiology. These possibly underpin the greater risk of renal and cardiovascular disease (CVD) in men and, conversely, confer the relative protection from these conditions in women, at least until menopause. In recent years, advances have been made in understanding the mechanistic bases for sex-related differences in CVD and these have been reviewed in detail. Therefore, the purpose of this report is to provide an update of findings in the past few years.

Sex-Specific Risk Factors and Clinical Outcomes

Increasingly, studies are incorporating sex as a factor into their analyses. Although not all studies demonstrate a sex-specific interaction, many do, exemplifying the mantra, seek and ye shall find; this appears to be particularly true for sex-related differences in CVD. In recent years, evidence that women have smaller and stiffer hearts because of a greater collagen content has received a good deal of attention for the reason that it may explain some of the puzzling differences in clinical signs of CVD between men and women. Puntmann et al8 examined aortic stiffness by pulse wave velocity and ventricular deformation indices using MRI both at rest and during dobutamine challenge in elderly men and women. At rest, women had greater aortic stiffness and ventricular deformation than men. Moreover, sex-related differences were observed during stress because men had increased longitudinal and circumferential ventricular deformation during dobutamine challenge, whereas women only had an increase in circumferential deformation.8 These data suggest that differential loading of the aortic reservoir in men occurs because of increases in longitudinal and circumferential ventricular contraction, an effect independent of aortic stiffness. However, dynamic challenge with dobutamine induced only a limited response in women, because although men could improve longitudinal ventricular contraction, women could not. Russo et al9 reported similar findings of increased arterial stiffness and wave reflection in women compared with those in men. In addition, an inverse relationship between arterial stiffness and left ventricular diastolic function was identified in both sexes. Therefore, higher arterial stiffness may contribute to the greater risk of developing heart failure in the presence of a normal ejection fraction in women. In both men and women, there is a linear increase in arterial stiffness with aging. Although women have increased arterial stiffness, this may be somewhat tempered by female sex steroids during the reproductive years. Following menopause, there is a profound acceleration in arterial stiffening, probably underpinning the disproportional increase in heart failure and systolic hypertension in elderly women.10

Sex-Related Differences in the Trajectory of Arterial Pressure With Age

The tracking of arterial pressure with age has been firmly established and there are well-established sex-related differences in these relationships.11,12 Moreover, the trajectory of the relationship between age and arterial pressure is influenced by birth weight and growth in childhood.13

Indeed, in a recent large-cohort study, linear growth velocity (height) between 8 and 13 years in boys was shown to be positively associated with adult arterial pressure.14 This relationship was suggested to be linked with the early onset of puberty and increases in testosterone in boys because this association was not present in girls. Moreover, Pausova et al15 have shown sex-related differences in the relationship between the distribution of body fat and arterial pressure in adolescence. In a population-based study, a strong positive relationship was observed between arterial pressure and visceral fat in boys.15 In contrast, in adolescent girls, arterial pressure was more strongly linked with total body fat rather than visceral fat.15 Thus, the trajectory of arterial pressure can be influenced early in life, increasing the risk of CVD in adulthood.

Furthermore, in aging populations, pulse pressure has been shown to be positively associated with risk of CVD in both men and women, but the trajectory has been found to be steeper with age in women.18 Finally, in women, late-life dementia has been shown to be positively correlated with midlife systolic pressure.19 In sum, these dimorphic functional patterns suggest that the mechanisms underlying the development of CVD are sex specific, and accordingly, clinical management may require therapies that have been tailored for the sexes.
A strong relationship among birth weight, renal size, nephron number, albuminuria, and systolic blood pressure has been shown in several racial groups. Animal studies have recapitulated these findings and allowed exploration of the underlying mechanisms, which are sexually dimorphic. Testosterone has been clearly demonstrated to contribute to the programming of adult hypertension in growth-restricted male rat offspring. Recently, this same group has defined a role for increased oxidative stress in determining kidney function and arterial pressure in growth-restricted male offspring, an effect that was reversed by antioxidant therapy. We found that growth-restricted male rat offspring have an exacerbated cardiovascular phenotype compared with their female counterparts. Males exhibit increased arterial stiffness, impaired endothelium-dependent and endothelium-independent vasodilatation, reduced nephron endowment, and hypertension. Although growth-restricted female offspring have a nephron deficit, they are relatively protected, being normotensive even in aging, and do not exhibit the widespread endothelial dysfunction and vascular-stiffening characteristic found in male rats. Recently, it has been demonstrated (1) that the GPR30 (G-protein–coupled receptor 30) receptor, which has multiple effects, acts to reduce oxidative stress and improves renal function in mRen2.Lewis female rats through an estrogen-dependent mechanism and (2) that testosterone upregulates nicotinamide adenine dinucleotide phosphate oxidase, thus increasing oxidative stress. It is therefore likely that adaptations in cardiovascular function, including upregulation of oxidative stress, are involved in the fetal programming of disease but that female rats have mechanisms that are protective against these adverse effects, at least during the reproductive years.

Renin–Angiotensin System

Major sex-related differences exist in the renin–angiotensin system (RAS) because of differential modulation of this system by sex hormones. Estrogen regulates all components of the RAS, increasing the synthesis of angiotensin, while decreasing the synthesis and activity of renin and angiotensin-converting enzyme. Estrogen decreases the expression of the angiotensin type 1 receptor (AT₁R) in target tissue but has the opposite effect on the type 2 receptor AT₂R expression. In rat kidneys, ovariectomy decreased and estrogen replacement increased AT₂R expression. On the contrary, testosterone amplified the pressor RAS in males. This strongly suggests differential roles for these pathways between the sexes, with the balance shifted toward the depressor RAS pathways in females.

Clinically, there are sex-related differences in the regulation of arterial pressure and renal function by the RAS, and although some studies have reported sex-related differences in response to inhibition of the RAS, others have not. Yet, it should be recognized that many clinical trials are not powered to detect such differences because of the lower enrolment of women. However, animal studies have provided stronger evidence of sex-related differences in the RAS, suggesting that further clinical studies are warranted.

Our own studies in animal models have demonstrated an enhanced role for AT₂R in the regulation of arterial pressure in females. We showed that chronic infusion of angiotensin II (Ang II) at a low dose, paradoxically, decreases arterial pressure in female rats, at a dose that caused an increase in arterial pressure in male rats, through an AT₁R-mediated, estrogen-dependent mechanism. More recently, we extended these findings to AT₂R-knockout mice, demonstrating that the chronic pressor response to Ang II was attenuated in female wild-type mice compared with male wild-type and female AT₂R-knockout mice. These findings illustrate the dual nature of Ang II on arterial pressure control and support an enhanced role for AT₂R in regulating arterial pressure in females.

Sex-related differences in the regulation of renal function by the RAS also exist. Long-term arterial pressure regulation is inextricably linked to the renal excretion of salt and water, and derangements in renal tubular and hemodynamic function, which compromise the ability of the kidneys to maintain sodium and water homeostasis, are central to the pathophysiology of hypertension. Indeed, key components of the RAS are expressed throughout the kidney, and extensive evidence from our laboratory, and that of others, indicates that the RAS modulates renal excretory and hemodynamic function. Studies in normotensive and hypertensive rats have shown that females demonstrate a protective leftward shift in the pressure–natriuresis curve such that they excrete the same amount of sodium as males at a lower arterial pressure. We, and others, have detected differential expression of AT₂R in male and female kidneys, with a lower AT₁R/AT₂R ratio in females, suggesting that AT₂R may play a sex-specific role in the regulation of renal function. In support of this conjecture, in rats, we showed that although AT₂R modulates pressure–natriuresis in both sexes, AT₂R plays an additional protective role in the female renal vasculature. AT₂R maintains autoregulation of renal blood flow and glomerular filtration rate at low renal perfusion pressures in females and protects against the vasoconstrictor effects of Ang II. The sensitivity of the tubuloglomerular feedback mechanism, which is an important regulator of glomerular filtration rate, to Ang II is also reduced by the presence of AT₂R in female, but not male, mice. Finally, we have also provided evidence that direct AT₂R stimulation, with the AT₂R agonist Compound 21, produces renal vasodilation and natriuresis in male and female normotensive rats. AT₂R may, therefore, represent a valuable therapeutic target for the treatment of renal disease and CVDs in both men and women.

Evidence is also emerging that the angiotensin-converting enzyme 2/Ang(1–7)/Mas receptor (MasR) axis elicits sex-specific effects in the kidney. We have identified greater expression of renal angiotensin-converting enzyme 2 and MasR genes in female versus male normotensive rats, therefore further shifting the balance of the RAS to the depressor arm in females. In addition, Sullivan et al identified greater renal cortical levels of Ang(1–7) in female versus male spontaneously hypertensive rats, both basally and after exogenous Ang II infusion, in addition to increasing MasR expression in the renal cortex following Ang II infusion in female spontaneously hypertensive rats only. Furthermore, we showed in acute studies in normotensive rats that, similar to AT₂R, MasR might also play a sex-specific role in the renal vasculature as renal blood flow decreased significantly in female but not male rats when MasR was blocked.
Thus, there is evidence that responses to activation of the RAS are sexually dimorphic. Equally, there is strong evidence that other mechanisms of cardiovascular control\textsuperscript{46-48} differentially regulate cardiovascular function in the sexes. Understanding intrinsic sex differences in cardiovascular function has exposed new therapeutic targets and will continue to do so.

**Sympathetic Nervous System**

The potential for sex to modulate the integrative neural control of the cardiovascular system is beginning to emerge. Greater age-related increases in sympathetic activity and arterial pressure have been documented in women.\textsuperscript{49} Recent evidence also suggests that sympathetic activation is linked to the menstrual cycle, estrogen being sympathoinhibitory and progesterone being sympathoexcitatory.\textsuperscript{50} Indeed, estrogen receptors, specifically estrogen receptor β, in the paraventricular nucleus and rostroventromedial medulla have been recently shown to mediate the protective actions of estrogen to attenuate aldosterone/high salt–induced hypertension in mice by blunting sympathetic activation.\textsuperscript{51}

In young men, muscle sympathetic nerve activity is correlated with total peripheral resistance and inversely related to cardiac output. These relationships do not exist in young women, demonstrating fundamental sex-related differences in the mechanisms regulating blood pressure.\textsuperscript{52} Enhanced sympathetic outflow has been implicated in the development of hypertension associated with intrauterine growth–restriction in male rats.\textsuperscript{53} In comparison, intrauterine growth–restricted female rats are normotensive after puberty but develop hypertension with aging, which also corresponded with increased circulating leptin and increased visceral and total adiposity. The hypertension was ameliorated with bilateral renal denervation, indicating that it was underpinned by increased sympathetic activity.\textsuperscript{54} Sex-related differences in sympathetic responsiveness at the neuromuscular junction exist. Vasoconstrictor responses to adrenergic nerve stimulation are larger in males than in females, with the differences resolved with ovarectomy.\textsuperscript{55} Thus, the decline in the influence of the sex hormones on neurovascular constriction with aging will facilitate increased responsiveness of the vasculature to sympathetic activity. Understanding the interaction of sympathetic outflow with sex hormones may shed light on the causes behind the surge in hypertension in women after menopause.

**Conclusions**

Sexual dimorphism in, and the effects of sex steroids on, genetic, hormonal, and biochemical pathways sculpt cardiovascular function in men and women. Thus, in pursuit of mechanisms key to cardiovascular regulation in health and disease, it is imperative that studies be pursued in both sexes. Momentum is gaining in the reporting of sex-related differences in cardiovascular function. There are now data describing significant differences in large-artery and cardiac function between the sexes, which generally indicate that the clinical signs and symptoms of heart failure are sex dependent. Recent revelations that the role of AT\textsubscript{2}R is enhanced in female subjects may open up new therapeutic strategies directed at the heart, kidney, and vasculature. Evidence is beginning to emerge that significant sex-related differences in the integrative neural control of the cardiovascular system exist. The development and progression of hypertension, a major risk factor for CVD, differs between the sexes. Understanding these fundamental processes will lead to the identification of novel therapeutic targets for the maintenance of cardiovascular health in both men and women.

**Sources of Funding**

This study was supported by National Health and Medical Research Council (NHMRC) People support grant #490918 and NHMRC Project grants #490919 and #606652.

**Disclosures**

None.

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Hypertension. 2013;62:674-677; originally published online August 26, 2013;
doi: 10.1161/HYPERTENSIONAHA.113.00922

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

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World Wide Web at:
http://hyper.ahajournals.org/content/62/4/674

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